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ORIGIN OF ANOMALOUS SHIFT ADDITIVITY IN RIGID SATURATED MOLECULES

NMR SPECTRA OF SECONDARY SUBSTITUTED ADAMANTANES, PART III

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Abstract—A number of chemical shift data of α-protons of 2,4-disubstituted adamantanes are given and the effects of the substituents on the chemical shift of protons (substituent shift) are calculated in several ways. These data show that there is a mutual interaction of the substituents leading to a change in their screening parameters and resulting in an additional change in the chemical shift of the protons. The total substituent shift subdivides into two parts, one directly due to the substituent, and the other to a change in the screening parameters of bonds and atoms in the direct environment of the considered proton. The relative contribution of each of these mechanisms is evaluated with statistical methods. Many cases of anomalous shift behaviour observed in other rigid saturated molecules, as described in the literature, are clarified by this combined shift mechanism.

INTRODUCTION

ADAMANTANES are, due to their rigidity and the non distorted chair conformation of the 6-membered rings, ideal cases to investigate substituent shifts and substituent shift additivity. Fort and von R. Schleyer[1] have determined the substituent shifts in a number of 1-substituted adamantanes and when applied to 1,3-disubstituted adamantanes, 1,3,5-trisubstituted adamantanes and 1,3,5,7-tetrasubstituted adamantanes, they found good agreement between observed and calculated chemical shifts (rms. dev. 0·057 ppm, $\nu = 74$*).

Van Deursen *et al.*[2] have determined the substituent shifts in a number of 2-substituted adamantanes and when applied to 2,4-dihalosubstituted adamantanes, after removing the uncertainties in the substituent shifts, good agreement between observed and calculated chemical shifts was also found[3] (rms. dev. 0·040 ppm, $\nu = 56$) except for the protons geminal to the substituents, of which the rms. dev. is as much as 0·20 ppm ($\nu = 9$). This deviation of substituent additivity gave rise to further investigation into substituent shifts of the α-protons (using the data of additional 2,4-disubstituted adamantanes) and to a statistical evaluation of the shift data from the literature.

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* All the root mean squared deviations (rms. dev.) are calculated according to $\{1/\nu \sum_{i=1}^{n} (C_i - O_i)^2\}^{\frac{1}{2}}$, in which C_i is the calculated shift, O_i the observed shift, n the number of observations and ν is the number of degrees of freedom ($n-p$), in which p is the number of parameters estimated from the observed shifts to determine the calculated values.

RESULTS

For a number of 2,4-disubstituted adamantanes,[4] measured in deuterochloroform, the chemical shifts of the α-protons are given in Table 1. The chemical shifts of the α-protons and of the 4-protons of 2-monosubstituted adamantanes are given in Table 2. From these data the substituent shifts due to γ-substituents are calculated as given in Table 3. The data are separated into three series depending on the stereochemical configuration of the considered proton and the γ-substituent (Tables 4, 5, 6).

DISCUSSION

From Tables 4, 5 and 6 it is found that the γ-substituent shift largely depends on the nature of the α-substituent. The strongest deviation appears in the case of equatorial γ-substituents (Table 4 and 5). For instance the 2e-bromine seems to deshield with 0·10 ppm the 4a-proton in 2-bromoadamantane, whereas the 2e-bromine seems to shield this proton with 0·22 ppm in 2e-bromo-4e-iodoadamantane. Besides a small solvent effect this can only be explained by a mutual interaction between the substituents. This mutual interaction between α- and γ-substituents in adamantanes was already known from the kinetic behaviour of some adamantanes: the rate of the solvolyses of a tertiary bromine depends very strongly on the nature of the γ-substituent;[7, 8] the exchange of bromine for chlorine in 2-bromoadamantane in concentrated hydrochloric acid, does not occur with 2e-bromo-4e-aminoadamantane;[5] the isomerisation of a secondary OH group to a tertiary position in conc sulphuric acid, which occurs in the case of 2-hydroxyadamantane, does not occur in the case of 2e,4e-dihydroxyadamantane, 2e,4a-dihydroadamantane and 4e-hydroxyadamantanon-2.[9]

The mutual interaction of the substituents considerably affects the use of the substituent shifts and the subsequent calculations. This interaction apparently changes the screening parameters of the substituents.

It seems appropriate to split the total substituent shift into two parts. The part due to the substituent itself, i.e. the combination of well known screening parameters such as magnetic anisotropy and electric field effects, will be called δ(direct). The part due to a change in screening parameters in other bonds and atoms, induced by the substituent, will be called δ(indirect). Thus the total substituent shift δ(subst) can be represented as

$$\delta(\text{subst}) = \delta(\text{direct}) + \delta(\text{indirect}).$$

Although the term δ(direct) will be modified by the mutual interaction, in a first approximation it is a constant for a certain (γ) substituent, because the rms. dev. between observed and calculated chemical shifts of all protons except the geminal ones in 2,4-dihaloadamantanes is low[3] (rms. dev. = 0·04 ppm, $\nu = 56$). If we select the chemical shifts of those secondary protons in 2,4-dihaloadamantanes, of which the total observed substituent shift is greater than 0·50 ppm,[3] the rms. dev. is still only 0·034 ppm ($\nu = 12$) (average total substituent shift: 0·65 ppm). From this rms. dev. and the average total substituent shift (av. sh.) it can be concluded that the change in δ(direct) may amount to about 5%.

Concerning the δ(indirect) term, it is obvious that a change in screening parameters of bonds and atoms in the direct environment of the considered proton will give the largest contribution to the δ(indirect) term, i.e. in particular α bonds and atoms (α-environment). The question arises as to how far the β-environment also contributes to the δ(indirect) term. An indication of a contribution of the β-environment is found in the rms. dev. $= 0{\cdot}088$ ppm of the 3-protons of 2,4-dihaloadamantanes ($\nu = 6$) (av. sh.: 0·49 ppm), the 3-proton being β to both the substituents. However, the rms. dev. of the shifts of the 1- and 5-protons, which are β to only one of the substituents, is 0·025 ppm ($\nu = 9$, av. sh.: 0·26 ppm), which is less than that of the secondary protons.

The same behaviour is observed in 1,3-disubstituted adamantanes,[1] in which the rms. dev. of all the protons is 0·056 ppm ($\nu = 45$) and that of the protons which are β to one and two substituents is 0·049 ppm ($\nu = 18$) and 0·064 ppm ($\nu = 9$) respectively. So there is no significant contribution of the β-environment to the δ(indirect) term and therefore, by approximation only the α-environment contributes to this term.

It is obvious from the Tables 4 and 5 that in these γ-substituent shifts the δ(indirect) term predominates over the δ(direct) term. Consider again the equatorial γ-bromine shift on the axial proton (Table 4). With a change in the α-environment on the part of only one of the three α-atoms, the γ-bromine shift changes from $+0{\cdot}10$ to $-0{\cdot}22$ ppm, i.e. a change in the δ(indirect) term of 0·32 ppm, which exceeds the total substituent shift.

TABLE 1. CHEMICAL SHIFTS OF THE PROTONS GEMINAL TO THE SUBSTITUENTS IN 2,4-DISUBSTITUTED ADAMANTANES[a]

Substituents		2e, 4e disubst.		2e, 4a disubst.		Footnotes
2	4	2a	4a	2a	4e	
Cl	Cl	4·26	4·26	4·82	4·51	*b, e*
Br	Br	4·50	4·50	5·15	4·73	*b, e*
I	I	4·89	4·89	5·48	4·96	*b, e*
I	Br	4·78	4·60			*g*
Br	Cl	4·50	4·23	5·00	4·45	*c, d*
OH	OH	3·75	3·75	4·18	3·97	*c,f*
OH	Cl	3·85	4·23			*e*
OH	Br	3·88	4·45			*e*
NH_2	Cl	3·03	4·33			*c*
NH_2	Br	3·01	4·57			*c*
NH_2	I	3·15	4·82	3·63	5·05	*e*
$NHCOCH_3$	Cl	4·06	4·36			*e*
$NHCOCH_3$	Br	4·12	4·59			*e*
$NHCOCH_3$	I	4·19	4·84			*e*
$OCONH_2$	OH			5·09	4·03	*g*
=O	OH		3·95		4·28	*g*
=O	$OCONH_2$		4·83		5·14	*g*
=O	Cl		4·33		4·65	*h*
=O	Br		4·55		4·82	*h*
=O	I		4·73		4·98	*h*

[a] Measured on a Varian HA 100 as a solution in deuterochloroform, with TMS as internal reference, unless otherwise stated.

[b] Data from Ref. 3.

[c] Original data from A. C. Udding (Ref. 5), measured on a Varian A-60.

[d] Measured in CCl_4.

[e] The data differ slightly from those measured by A. C. Udding (Ref. 5).

[f] Some DMSO was added to the solution.

[g] Unpublished compounds.

[h] Data from Ref. 6.

One of the consequences of the δ(indirect) term is that data of substituent shifts may be applied only in cases of identical α-environment, because the δ(indirect) term depends both on the nature of the substituent and on the nature of the α-environment. With another α-environment a different set of substituent shifts will be found.

Such a δ(indirect) term is not only to be found in adamantanes. In many cases where anomalous shifts were observed, non-identical α-environments were encountered, whereas identical α-environments were paired with good substituent shift additivity. Some of these cases will be reviewed here:

TABLE 2. CHEMICAL SHIFT OF SOME PROTONS IN 2-MONOSUBSTITUTED ADAMANTANES[a]

Substituent		Configuration of substituent postulated to be		
		2-eq.		2-ax.
	α-H	4-ax H	4-eq H	4-ax H
Cl	4·39	1·78[c]	1·94[c]	2·27
Br	4·68	1·85[c]	1·97[c]	2·33
I	5·00	1·95	1·95	2·38
OH	3·85[b]	1·69	1·82	2·06
NH_2	2·98	1·77[d]	1·77[d]	1·95
$NHCOCH_3$	4·08	1·79[d]	1·79[d]	
$OCONH_2$	4·78	1·79[d]	1·79[d]	2·00
=O		2·03[d]	2·03[d]	

[a] Measured on a Varian HA-100 as a solution in deuterochloroform, with TMS as internal reference. Most of these data are from Ref. 2.

[b] The chemical shift given in Ref. 2 is wrong.

[c] These data are corrected according to Ref. 3.

[d] These data are approximations due to overlapping lines.

(a) Zürcher[10] has shown that the substituent shifts for the tertiary methyl groups in steriods are additive (rms. dev. = 0·022 ppm, ν = 180).

The substituent shifts can be well correlated with screening parameters as electric field effects and/or magnetic anisotropy effects.[11] These screening parameters can also be applied to the tertiary methyl groups of bornanes (rms. dev. 0·033 ppm, ν = 26). In all these cases the β-environment and the α-environment are identical. However, when these screening parameters are applied to the 3-*exo* and 3-*endo* (methylene) protons of 2-substituted norbornenes, which has a different α-environment, a relative large correction term must be added.[12]

(b) The substituent shifts of the α-protons derived from CH_3X differ from those derived from CH_3CH_2X and from $(CH_3)_2CHX$. Cavanaugh and Daily have introduced a C—C bond shift to explain the deviation.[13]

(c) The substituent shifts of the secondary substituted adamantanes differ from those of the tertiary substituted adamantanes (2, 3, Table 5), and both differ from the substituent shifts derived from steroids and cyclohexanes.[14]

(d) Eliel *et al.*[15] have determined the substituent shifts due to alkyl groups of the carbinol proton of cyclohexanols, and as long as these shifts are applied to carbinol protons of conformational well defined secondary alcohols, a very good agreement between observed and calculated chemical shift is found (rms. dev. = 0·024 ppm, ν = 23),[15] (rms. dev. = 0·035 ppm, ν = 6).[16] However, when these substituent shift

TABLE 3. CALCULATION OF THE SUBSTITUENT SHIFTS

Configuration of		Calculation	Results in Table
Substituent	Proton		
e	a	$4a(4e\alpha, 2e\gamma)^a - 2(2\alpha)^b$	IV
		$2a(2e\alpha, 4e\gamma) - 2(2\alpha)$	
e	e	$4e(4a\alpha, 2e\gamma) - 2(2\alpha)$	V
a	a	$2a(2e\alpha, 4a\gamma) - 2(2\alpha)$	VI

e = equatorial α = α substituent given with position.
a = axial γ = γ substituent and configuration.

[a] Is chem. shift of 4a proton with a 4e, α-substituent and a 2e, γ-substituent.

[b] Is chem. shift of 2-proton with a 2α-substituent, without the γ-substituent. When the α-substituent is H, $2(2\alpha) = 1·75$, i.e. the chemical shift of secondary protons in adamantane.

data are applied to the methylene protons of 1,3,5-trimethylcyclohexanes, deviations of as much as 0·5 ppm are observed between experimental and calculated chemical shifts.[18] Recently Remijnse *et al.*[17] obtained the chemical shifts of equatorial-methylcyclohexane from which the eq-methyl substituent shifts on the methylene protons can be calculated. When these substituent shifts are applied to the methylene protons of 1e, 3e, 5e-trimethylcyclohexane, the observed and calculated shifts agree within 0·03 ppm.

ApSimon *et al.* have used the substituent shift data from the carbinol proton to calculate the diamagnetic anisotropy of the C—H and C—C bond. However, using the chemical shift data of cyclohexane and ethane, another set of magnetic anisotropy data was found.[19] Application of both sets of magnetic anisotropy data to the calculation of the diamagnetic anisotropy of the C=C bond shows that the second set of data gives less scattering in the results.[20]

So generally a δ(indirect) term has to be considered. We have calculated the α substituent shift (Table 7) from the chemical shift data of the Tables 1 and 2, in an attempt to gain some insight about the mutual interaction of the substituents. With a particular α-substituent the α-environment remains constant, so the δ(indirect) term

TABLE 4. THE SUBSTITUENT SHIFT OF AN AX. PROTON DUE TO AN EQ. γ-SUBSTITUENT IN DEPENDENCE OF THE EQ. α-SUBSTITUENT IN ADAMANTANES[a]

	eq. γ-Substituent						
eq. α-Substituent	OH	NH_2	$NHCOCH_3$	Cl	Br	I	=O
H	−0·06	0·02	0·04	0·03	0·10	0·20	0·28
OH	−0·10			0·00	0·03		0.10
$OCONH_2$							0·05
NH_2				0·05	0·03	0·17	
$NHCOCH_3$				−0·02	0·04	0·11	
Cl	−0·16	−0·06	−0·03	−0·13	−0·16		−0·06
Br	−0·23	−0·11	−0·09	−0·18	−0·18	−0·08	−0·13
I		−0·18	−0·16		−0·22	−0·11	−0·27

[a] A negative sign means an upfield shift.

Table 5. The substituent shift of an eq. proton due to an eq. γ-substituent in dependence of the ax. α-substituent[a]

ax. α-Substituent	eq. γ-Substituent OH	NH_2	Cl	Br	I	=O
H	0·07	0·02	0·19	0·22	0·20	0·28
OH	0·12					0·43
$OCONH_2$						0·36
Cl			0·12	0·06		0·26
Br				0·05		0·14
I		0·05			−0·04	−0·02
"adamantane"[b]	0·24		0·23	0·20	0·09	

[a] A negative sign means an upfield shift.

[b] The substituent shift of a 3-proton in 1-substituted adamantane (Ref. 1).

will vanish. The differences in substituent shift of a particular α-substituent are only due to a change in its δ(direct) term, this change being induced by the γ-substituent. Although the absolute differences in the α-substituent shifts are of about the same magnitude as those in the γ-substituent shifts, the relative rms. dev. from the average shift is much smaller, i.e. 4·3 % ($\nu = 48$). This is of about the same magnitude as already calculated for a relative change of the δ(direct) term. Because the differences in the α-substituent shifts are mainly due to a change in the δ(direct) term alone, these differences must give an indication as to the kind of mutual interaction. According to the discussion of Dewar *et al.*,[21] in a system with exclusively σ bonds, only inductive and field effects would contribute to the interaction. If so, the differences in the α-substituent shifts ought to correlate with the electronegativity of the γ-substituent, which is not the case. For instance the trend of the α-bromine substituent shift in the case of diequatorial substituents is $H > NH_2 = NHCOCH_3 > OH > Cl > Br = I$. Thus the nature of the interaction is not clear for the moment.

Table 6. The substituent shift of an ax. proton due to an ax. γ-substituent in dependence of the eq. α-substituent[a]

eq. α-Substituent	ax. γ-Substituent OH	Cl	Br	I
H	0·31	0·52	0·58	0·63
OH	0·33			
$OCONH_2$	0·31			
NH_2				0·65
Cl		0·43		
Br		0·32	0·47	
I				0·48

[a] A negative sign means an upfield shift.

TABLE 7. THE SHIFT OF A PROTON DUE TO ITS α-SUBSTITUENT IN DEPENDENCE OF THE γ-SUBSTITUENT

	Orientation	Orientation				α-Substituent				
γ-Substituent	α-substituent	γ-substituent	NH_2	OH	$NHCOCH_3$	$OCONH_2$	Cl	Br	I	
H	—	—	1·23	2·10	2·33	3·03	2·62	2·93	3·25	
OH	eq	ax		2·12		3·03				
Cl	eq	ax					2·55	2·73		
Br	eq	ax						2·82		
I	eq	ax	1·25						3·10	
NH_2	ax	eq							3·28	b
OH	ax	eq		2·15						
$OCONH_2$	ax	eq		2·24						b
Cl	ax	eq					2·57			
Br	ax	eq					2·48	2·76		
I	ax	eq							3·01	
=O	ax	—		2·25		3·11	2·58			b
NH_2	eq	eq					2·56	2·80	3·05	b
OH	eq	eq		2·06			2·54	2·76		
$NHCOCH_3$	eq	eq					2·57	2·80	3·05	b
Cl	eq	eq	1·25	2·07	2·28		2·48	2·72		
Br	eq	eq	1·16	2·03	2·27		2·38	2·65	2·93	
I	eq	eq	1·20		2·24			2·65	2·94	
=O	eq	—		1·92		2·80	2·29	2·47		b

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[b] These data are approximations due to inaccurate knowledge of the chemical shift of the relevant proton of the 2-monosubstituted adamantane.

CONCLUSIONS

The chemical shift data of adamantanes as well as those of other compounds clearly show that, in addition to the well known causes of substituent shifts, an indirect shift mechanism must be considered, that is the change in the screening parameters of bonds and atoms in the direct environment of the considered proton induced by the substituent.

Hence the application of substituent shifts is limited to those cases in which the direct environment of the considered protons is the same in each case.

More data will be required if we are to understand the nature of the indirect shift term in greater detail.

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